UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 15 2016

The Honorable Charles E. Grassley
Chairman
Committee on the Judiciary
United States Senate
Washington, D.C. 20510

OFFICE OF
RESEARCH AND DEVELOPMENT

Dear Mr. Chairman:

Thank you for your letter dated June 14, 2016, to the Administrator of the United States Environmental Protection Agency regarding the use of human subjects in controlled exposure research conducted by the EPA's Clinical Research Branch, which is part of the National Health and Environmental Effects Research Laboratory (NHEERL). NHEERL is a part of the Office of Research and Development.

The EPA is required by law to establish National Ambient Air Quality Standards (NAAQS) to protect the public health with an adequate margin of safety. The EPA is committed to ensuring that the NAAQS and other regulatory benchmarks are supported by the best science. Accordingly, the EPA uses many different research approaches to obtaining scientific data.

The EPA review process for human subjects research exceeds what is generally accepted and required by universities, industry, and other government agencies. Controlled human exposure studies conducted at EPA's NHEERL undergo up to 13 levels of both internal and external review. As you note in your letter, the EPA is governed by the "Common Rule" for all research that involves human subjects and The EPA has codified that regulation at Title 40 C.F.R. Part 26, which also includes additional protections for vulnerable subjects in subparts B, C, and D.

As you also note, the EPA Office of Inspector General (OIG) conducted a review of our controlled exposure research in 2013-14, at the request of Congress. As a result of our extensive oversight process, the OIG found that the EPA followed all applicable laws, regulations, policies, procedures and guidance; obtained required approvals; and obtained informed consent as appropriate. As could be expected with any review of this kind, the OIG made recommendations for programmatic enhancements. Corrective actions associated with these recommendations were completed within established timeframes. While the recommendations were directed at enhancing the human studies that the EPA conducts at NHEERL, many of the recommendations were applicable beyond NHEERL and were therefore implemented agency-wide, where appropriate.

While we have already implemented the OIG recommendations, we also recognized that having independent experts provide guidance for the specific context of controlled exposure studies would further enhance the conduct of research at the EPA. As a result, the EPA charged the National Academy of Sciences (NAS) to convene a committee of subject matter experts to look at the complicated issues of risk and benefit in our exposure studies. While this external review and input

was not required, it reflects the EPA's commitment to continuous quality improvement and upholding the highest standards in research. The NAS report is expected in September of 2016.

Since 2006, there were 21 controlled human exposure studies led by the EPA during this time period, with some running for multiple years. Controlled exposure research helps to inform risk reduction, risk prevention and treatment strategies. Again, the EPA takes very seriously our commitment to upholding the highest standards in research. Controlled exposure of healthy human research volunteers to inhaled pollutants provides an important experimental approach capable of isolating pollutants for the purpose of identifying specific biological and physiological responses. These responses include measuring changes in these biomarkers predictive of future cardiovascular risk in susceptible individuals, such as those with asthma, chronic obstructive pulmonary disease, vascular disease, arrhythmia or heart failure. Moreover, biomarkers of inflammation and oxidative stress may serve to help identify individuals at greatest risk for adverse pulmonary and cardiovascular outcomes, to develop new pharmacological or interventional tools to mitigate biological responses and to monitor the efficacy of interventions.

Each controlled exposure study has strict eligibility requirements for participation. Potential participants are screened to ensure that they meet eligibility requirements before they are approved to participate in a particular study.

The results of these controlled exposure studies have had significant impact on advancing health science and protecting public health. For example, results from controlled exposure studies have contributed to the development and revisions in air quality standards for both ozone and particulate matter, and the identification of novel ways to mitigate or reduce the effects of pollutants on the body. In addition, all studies ultimately are analyzed and included in the Integrated Science Assessments (ISA) for each pollutant of interest. The studies in the ISA, in turn are reviewed by an outside body of scientists, as required by the Clean Air Act. Over the last ten years, an average of $3,017,932 annually was budgeted for support of these types of studies.

The regulations cited in your letter (Title 21 C.F.R. 50, Subpart B) are the Food and Drug Administration (FDA) requirements for informed consent, including the requirement to post applicable clinical trials on clinicaltrials.gov. In general, research at the EPA does not involve FDA-regulated products and is not subject to the FDA regulations. In particular, the studies conducted by the EPA are not "applicable clinical trials" as defined by the FDA, and are not required to be posted on ClinicalTrials.gov. However, the EPA is committed to the transparency and public availability of its science. Therefore, we have voluntarily submitted our controlled exposure studies to ClinicalTrials.gov, even though they are not "clinical trials" as envisioned by the FDA, testing a drug, device or biologic for the treatment of human health conditions.

The EPA uses many different areas of science when conducting research on or evaluating the effects of environmental pollutants on human health. These approaches include in vitro or laboratory studies, computer modeling, animal experiments, epidemiology or observational studies in humans, and controlled human exposure studies. In vitro and animal studies are generally cheaper, but they may not adequately predict the impact of real world exposures – such as multiple pollutant exposures at low levels – on human health. Large scale epidemiology studies are used to find associations between real world environmental exposures and human health effects, and these studies play an important role in furthering our understanding of the health effects of environmental pollutants. Other types of epidemiological studies, such as those that examine death certificates and other medical records, also provide important information that enable scientists to answer crucial questions about environmental health.

Controlled human exposure studies complement epidemiology studies by providing a better understanding of the pathophysiological mechanisms that are responsible for causing an adverse health event. Each of these types of studies plays an important role in EPA's work, and they are complementary. They each provide important components of the evidence base. From individual physiologic effects to population health impacts, these studies provide a strong scientific basis for public health decision-making.

Again, thank you for your letter. Please feel free to contact me if you have any questions, or your staff may contact Christina J. Moody in our Office of Congressional and Intergovernmental Relations at moody.christina@epa.gov or (202) 564-0260.

Sincerely,

Thomas A. Burke

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